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Spastic Paraplegia Associated with Addison's Disease: Adult Variant of Adreno-Leukodystrophy

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Summary. Clinical and pathological features of an adult variant of adreno-leukodystrophy (ALD) are presented. A male with clinical and laboratory signs of Addison's disease (AD) developed at age 22 a slowly progressing paraplegia with slight sensory deficits in both legs and bladder and sphincter dysfunctions; he died at age 24 in an AD crisis. Autopsy revealed hyperplasia of lymphatic tissues, lymphocytic infiltrates in various organs including the CNS and adrenocortical atrophy with prominence of large ballooned, sometimes bizarre and occasionally striated cortical cells. CNS lesions consisted in incomplete demyelination of long tracts of brain stem and spinal cord with accentuation in the pyramical tracts; in these areas, perivascular cuffs of "epitheloid" histiocytic cells contained a strongly PAS-positive non-sudanophilic material. Electron microscopy demonstrated massive storage of leaflet structures in perivascular histiocytes identical to the lamellar profiles previously described as specific for ALD. Some leaflets were found in close contact with compact lamellar arrays and with an electron-dense fingerprint material within astrocytes.

In our case, the spastic paraplegia-AD syndrome which has been described previously in several clinical observations could be neuropathologically classified as an adult variant of ALD. Several differences to "classical" ALD occurring in young boys are stressed: the predominance of the endocrine disorder probably accounting for some of the perivascular lymphocytic infiltrates within the CNS; the absence of both clinical and pathological signs of diffuse cerebral involvement and the peculiar topistic pattern of CNS lesions and the very slow evolution of neurological signs paralleled by the absence of active sudanophilic demyelinating lesions. The possible mechanism of demyelination and the nature of the suggested metabolic defect in ALD are discussed. The ultrastructurally prominent leaflet structures may originate from myelin remnants, thus relating ALD to pathological storage of a myelin degradation product.

Key words: Adreno-leukodystrophy — Adrenal gland diseases — Paraplegia — Spinal cord diseases — Metabolic diseases — Leukodystrophy — Demyelination.

Zusammenfassung. Klinische und pathologische Befunde einer adulten Form der Adrenoleukodystrophie (ALD) werden dargestellt. Ein Patient mit klinischem Bild und Laboratoriumsbefunden der Addison-Krankheit (AD) entwickelte im Alter von 22 Jahren eine sehr langsam zunehmende Paraspastik mit geringer Hypaesthesie in beiden Beinen und Blasen- und Mastdarmstörungen; er verstarb im Alter von 24 Jahren in einer AD-Krise. Bei der Autopsie fanden sich eine Hyperplasie des lymphatischen Apparats und lymphocytäre Infiltrate in verschiedenen Organen einschließlich des ZNS; beide Nebennieren waren atroph mit Hervortreten großer ballonierter, etwas bizarrer Rindenzellen mit gelegentlicher cytoplasmatischer Streifung. Im ZNS fanden sich pseudosystematische inkomplette Entmarkungen der langen Bahnen in Hirnstamm und Rückenmark mit Betonung der Pyramidenbahn, charakterisiert durch perivasale Manschetten „epitheloider" histiocytärer Zellen, die ein stark PAS-positives sudannegatives Material enthielten. Elektronenoptisch wurde eine massive Speicherung eines lamellären Materials in perivasalen Histiocyten nachgewiesen, welches mit den als spezifisch für die ALD angesehenen Einschlüssen übereinstimmte. Einige derartige Strukturen zeigten

einen engen Zusammenhang mit kompakten Lamellenaggregaten und mit einem elektronendichten „fingerprint"-Material innerhalb von Astrocyten.

In diesem Fall konnte das Paraplegie-AD-Syndrom, welches mehrfach bereits klinisch beschrieben worden war, aufgrund neuropathologischer Befunde als adulte Variante der ALD klassifiziert werden. Die Unterschiede dieser Form zur „klassischen" ALD, welche üblicherweise Knaben betrifft, werden hervorgehoben: das Überwiegen der endokrinen Symptomatik, was das Auftreten perivasaler Lymphocytensäume im ZNS zum Teil bedingen dürfte; das Fehlen klinischer und pathologischer Hinweise auf diffuse Beteiligung des Großhirns und die spezielle Topik der ZNS-Läsionen und die geringe Progredienz der neurologischen Symptomatik, welche im Einklang mit dem Fehlen florider sudanophiler Entmarkungsvorgänge steht. Der Mechanismus der Entmarkung und die Art der vermuteten metabolischen Störung bei der ALD werden diskutiert. Die elektronenoptisch charakteristischen lamellären Strukturen könnten aus dem Myelinabbau stammen, und damit könnte bei der ALD eine pathologische Speicherung eines Myelinabbauprodukts vorliegen.

Introduction

In recent years, the association of adrenocortical disease with diffuse cerebral sclerosis, usually called adreno-leukodystrophy (ALD) (Schilders's disease with melanoderma, melanodermic type leukodystrophy, sudanophilic leukodystrophy with Addison's disease), has become defined as a distinct nosological entity with characteristic clinical and pathological findings; the combination of a sex-linked recessive heredity with similar ultrastructural changes in many organs has been considered to be a generalized metabolic disorder (Powell et al., 1975; Schaumburg et al., 1975), although other authors have favored an autoimmune process causing both CNS and adrenal lesions (Gerhard et al., 1970; Forsyth et al., 1971). In the classical form, ALD affects only boys in the first two decades and leads to death usually in 1 to 3 years (Blaw, 1970; Ulrich and Isler, 1971), whereas ALD in adults is very uncommon. There have been several clinical descriptions of the combination of Addison's disease (AD) with spastic paraplegia (Neusser and Wiesel, 1910; Harris-Jones and Nixon, 1955; Hewitt, 1957; Penman, 1960; Schaumburg et al., 1975); since pathological examination was lacking in these cases, any relation of this peculiar syndrome to ALD has been a matter of speculation. We report in this paper on the clinical, light and electron microscopical findings in a case of AD associated with spastic paraplegia, which suggest the classification of this syndrome as an adult variant of ALD.

Case Report

The family history disclosed a rather dark skin pigmentation of the patient's otherwise normal mother; no neurological nor endocrinological abnormalities in other family members were reported. Patient L. Ned., a blond and blue-eyed male, suffered in childhood from frequent benign infections. Since adolescence, vasocirculatory dysregulation with episodes of collapse was frequent. Since age 8, first areolar, then diffuse alopecia was noted. Both mammary regions became enlarged at age 12, followed by generalized skin itching 4 years later. The patient was hyperpigmented since childhood; from age 20 on, skin color darkened to a bronze tinge accentuated in light-exposed regions. At age 22, progressive weakness in both legs was noted, accompanied by temporary cramp-like pains in both thighs and occasional muscle fasciculations in the upper arms and thighs. Subsequently, bladder and anal sphincter dysfunction developed; there was no impairment of sexual functions. At first admission to the Neurologic Clinic at age 24, 7 months before death, the patient showed a deeply bronzed

skin, diffuse alopecia including axillary and pubic hairs and a spastic gait with bilaterally exaggerated tendon reflexes of both lower extremities, bilateral extensor plantar responses and loss of abdominal reflexes. Motility of both legs was markedly diminished, movements were uncontrolled and propulsive. Both legs were hypaesthetic for all qualities with distal accentuation. The CSF data were normal. The EEG was abnormal with bilateral parietal 5—6 c/s theta-groups spreading in frontotemporal to temporal directions. Bilateral carotid arteriograms, pneumoencephalography, myelography and brain scan were normal. A biopsy of the slightly enlarged liver showed hemosiderosis and round cell infiltration in periportal areas without cirrhotic changes; a skin biopsy revealed marked melanin increase in the epidermal basal cell layer and chronic inflammatory infiltrates in the corium. Peripheral blood smears showed a lymphocytosis up to 66%; eosinophil granulocytes sometimes constituted up to 7% of white blood cells. Serum potassium was around 5.0 mval/l, sodium between 131 and 135 mval/l. Urinary excretion of 17-OH-corticosteroids was abnormally low (1.5 and 1.2 mg/24 h on two successive days), that of 17-ketosteroids rather low for a young male (13.0 and 8.5 mg/24 h). After ACTH stimulation neither 17-OH-corticoids (1.3 and 3.0 mg/24 h) nor 17-ketosteroids (14.0 and 17.0 mg/24 h) showed any significant rise, indicating primary adrenocortical insufficiency.

The spastic paraplegia, the slight sensory deficit and the bladder and anal dysfunctions persisted unchanged till death.

After a visit to a sauna bath 2 weeks before death, the patient detoriorated rapidly with circulatory collapse, vomiting, vertigo and impairment of consciousness alternating between agitated and soporific states. One week before death, the temperature rose to 38.5°C, and laboratory data showed rapidly progressing metabolic and electrolyte dysregulation; the blood pressure, formerly around 120/80, fell to 90/50 mm Hg, accompanied by tachycardia of 120/min. Death was caused by cardiovascular failure.

General Autopsy

The thymus was preserved in walnut-size; lymphoreticular tissues of the pharynx and paratracheal lymph nodes were proliferated. The adrenal glands measured 2.5:3:0.2 cm on right and 4:1.7:0.2 cm on left side and were hard and fibrous in consistency and chocolate-brown in colour, limits between cortex and medulla were not discernable; in the right adrenal gland two pea-sized brown nodules were found. All other endocrine and internal organs were unremarkable.

Histological Examinations of Various Organs

Adrenals. The normal adrenal structures were disorganized with an intact medulla surrounded by a fibrous capsule and abundant fatty tissue; cortical tissue without any zonal structures was preserved only in small areas (Fig. 1A). The cortical cells were of medium to large size and irregular plump shape with eccentric hyperchromatic nuclei lying in an eosinophil homogenous or granular cytoplasm; these cortical cells also made up the two larger adenomatous nodules in the right adrenal gland. In the cortical remnants very large "ballooned" cortical cells were prominent, having a diameter up to 120 μ and sometimes a bizarre appearance; the slightly granular eosinophilic cytoplasm was frequently ring-like, being condensed at the cell periphery (Fig. 1C) and showing occasional "striations" (Fig. 1B); these cells were faintly stained with Sudan black B and showed a variable PAS positive reaction. The connective tissue between cortical cell strands was increased and focally infiltrated by lymphocytes (Fig. 1A).

Liver. Slight to moderate lymphocytic infiltrations in periportal areas (Fig. 1D).

Thymus. Some lymph follicles without germinal center still preserved.

Myocard. Discrete lymphocytic infiltrations.

Skin. Strong increase of melanin pigment in basal cell layer of epidermis.

Spleen. Regular structure, but diffuse increase of lymphocytes.

Neuropathological Examination

Macroscopically, the brain was edematous (weight 1720 g); the pyramidal tracts of the brain stem and spinal cord showed a slight gray discoloration.

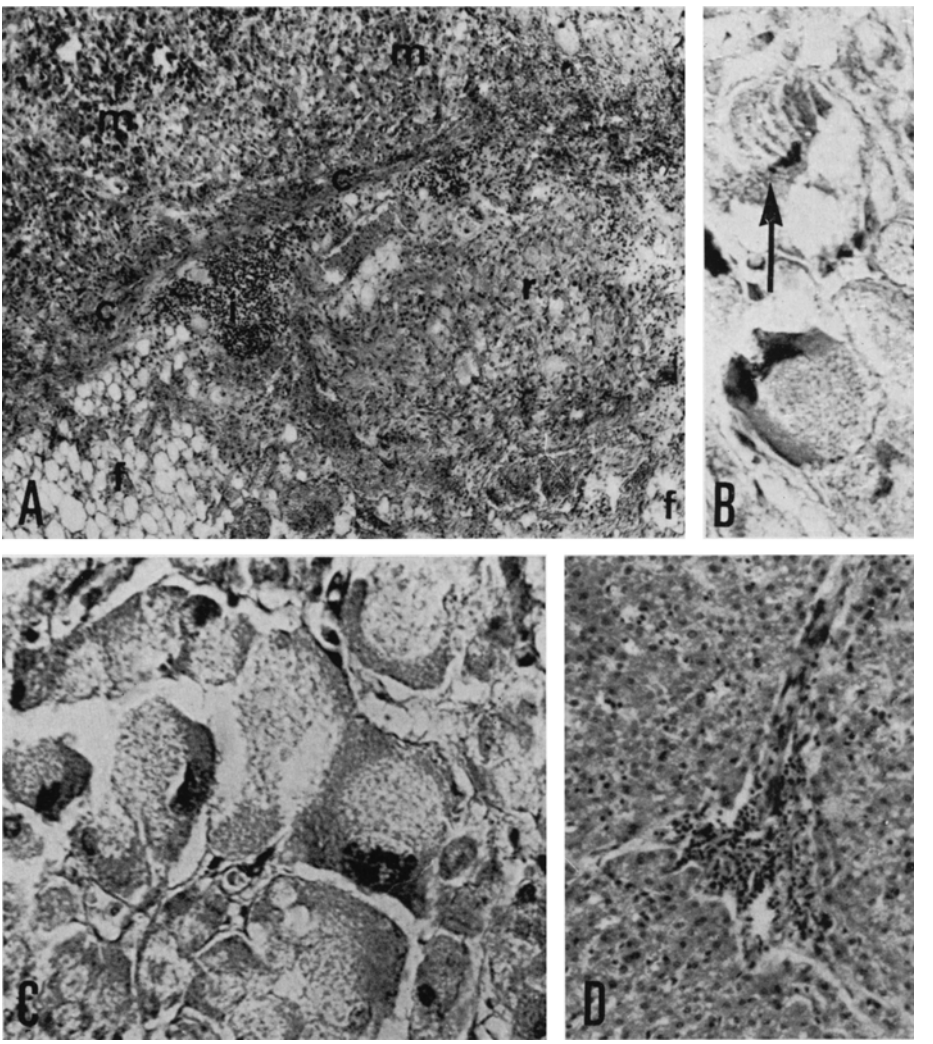

Fig. 1. (A)—(C) Adrenal gland. (A) Total disruption of adrenal structure with intact medulla (*m*) surrounded by fibrous capsule (*c*) and fatty tissue (*f*) and small areas of remnants of cortex (*r*); focal lymphocytic infiltration (*i*). Congo red × 48. (B) Ballooned cortical cell and striated cell (arrow). H.-E. × 300. (C) Large ballooned and occasionally bizarre cortical cells. Cv. × 300. (D) Liver. Moderate lymphocytic infiltration of periportal area. H.-E. × 120

Histological Examination

Formalin-fixed paraffin sections from numerous brain and spinal cord regions were stained with hematoxylin-eosin (H.-E.), cresylviolet (Cv.), sudan black B (SSB), PAS and Klüver-Barrera's, van Gieson's, Bodian's, Masson-Goldner's and Kanzler's methods; formalin-fixed frozen sections were stained with H.-E., SSB, Sudan III, PAS, alcian blue and acetic acid cresylviolet. Major changes were confined to the long tracts in the brain stem and spinal cord while sparing the white matter of the cerebral hemispheres. There was incomplete symmetrical demyelination of varying degree at different levels in the pyramidal tracts from the

cerebral peduncles to the lumbar cord, and accentuated in the pyramids of the medulla oblongata; in lesser degree similar symmetrical incomplete demyelination was found in the medial and lateral lemnisci, the brachium conjunctivum, the spinocerebellar tracts and the medial part of the posterior fasciculi (Fig. 2A). Axons were well preserved; there was no prominent loss of oligodendrocytes. In all demyelinated regions, small veins and capillaries were densely cuffed (Fig. 2B) by broad sheets of medium-sized (diameter 15—30 μ) histiocytic cells of "epitheloid" appearance with homogenous or, at high magnification, finely granular cytoplasm and an eccentric or central oval nucleus (Fig. 2D). The cytoplasm of these cells was stained intensely by PAS (Fig. 2H), but was weakly or non-metachromatic with acetic acid cresylviolet, negative with Sudan dyes (Fig. 2F) and partly anisotropic in polarized light (Fig. 2G), occasionally with linear cytoplasmic birefringence. In paraffin-embedded, PAS-stained sections occasional cytoplasmic "striations" (straight or curvilinear profiles) could be detected in some epitheloid cells (Fig. 2E). Histochemical features of these cells were similar both in frozen and paraffin-embedded sections. There was a moderate isomorphic gliosis with very large, sometimes bi- or trinucleated PAS-positive astrocytes in affected tissue; however, typical multinucleated globoid cells were not seen. Occasional perivascular lymphocytic cuffs were found, occurring also in non-demyelinated areas (Fig. 2C). The cerebral white matter including the internal capsules, was virtually unaffected with only very few scattered perivascular epitheloid cells; there and in the spinal cord, occasionally typical sudanophil perivascular macrophages were found, probably representing a discrete secondary antero- or retrograde degeneration of affected tracts; these macrophages differed both morphologically and histochemically (strong sudanophilia, weak or no affinity to PAS, strong anisotropism) from the epitheloid cells. Flourishing demyelination or breakdown was not found. The grey matter in all parts of the CNS was unremarkable, there were no signs of neuronal storage disease. Sections of the sciatic nerve were normal; sections from sural muscle showed discrete diffuse myopathic changes and occasional perivascular round cell infiltrates; signs of denervation atrophy were absent.

Electron Microscopical Examination

Formalin-fixed autopsy material from the severely affected oblongata pyramids was post-fixed in osmiumtetroxide and embedded in Epon. Most prominent were large perivascular histiocytic cells, obviously corresponding to the "epitheloid" cells found with the light microscope, with cytoplasmic storage of abundant lamellar material (Fig. 3A). This lamellar material either filled the cytoplasm almost completely (Fig. 3B at right) or was confined to circumscribed, pleomorphic aggregates (Fig. 3B at left), which may correspond to the cytoplasmic "striations" at the light optical level. At higher magnification, rather regular parallel arrays of lamellae of variable length were interspersed by occasional pleomorphic electron-dense bodies (Fig. 4A). High resolution revealed that the lamellar profiles consisted of two electron-dense membranes measuring about 25 Å in breadth (sometimes up to 60 Å when obliquely sectioned), usually separated by a rather regular electron-lucent space of about the same breadth (Fig. 4B); however, this central clear space sometimes had a more irregular configuration with a diameter up to 100 Å, showing adjacent broader and narrower segments (Fig. 4B arrowhead). In a few places, these irregularities increased to the formation of broad (diameter

Fig. 2A—H. CNS. (A) Myelin stains of rostral and caudal medulla oblongata and cervical and middle thoracic spinal cord. Demyelination of various degree in pyramidal tracts, medial lemniscus, spino-cerebellar tracts and fasciculus gracilis; spinal roots well myelinated. Kl.-B. $\times$ 2.5. (B) Numerous perivascular histiocytic cuffs in oblongata pyramid. Cv. $\times$ 48. (C) Pontine tegmentum; occasional perivascular lymphocytic cuffs. H.-E. $\times$ 120. (D) Oblongata pyramid; broad sheet of large histiocytic "epitheloid" cells around central capillary (arrow). H.-E. $\times$ 480. (E) Cytoplasmic "striations" in perivascular histiocyte. PAS $\times$ 1200. (F) Oblongata pyramid; absence of sudanophilic material in perivascular histiocytes. Frozen section. SSB $\times$ 120. (G) Cerebral peduncle; anisotropic material in perivascular histiocytes. Crossed polarizing filters. H.-E. $\times$ 480. (H) Cerebral peduncle; perivascular histiocytes intensely stained by PAS. PAS $\times$ 480

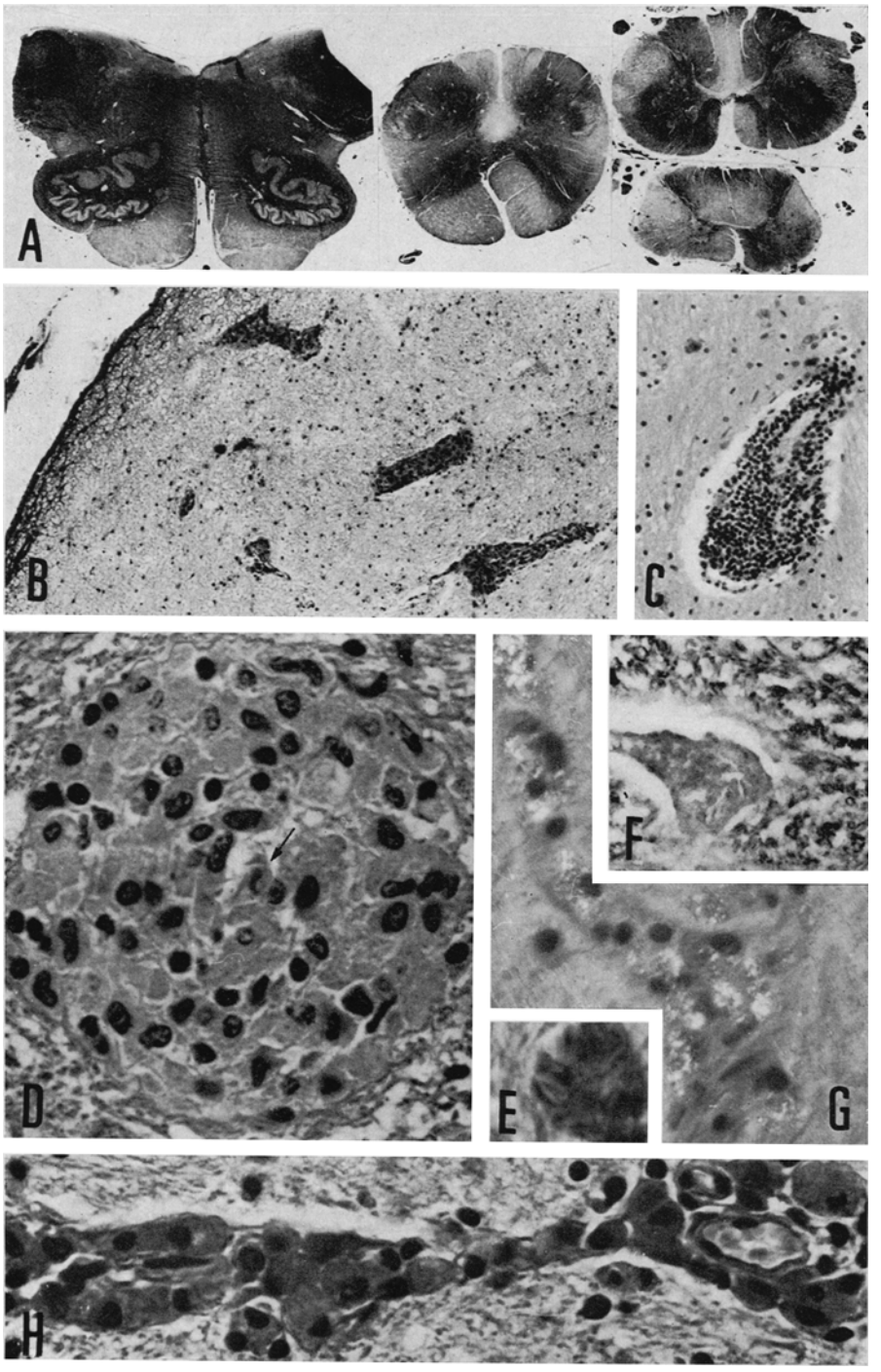

Fig. 2A—H (for legend see p. 241)

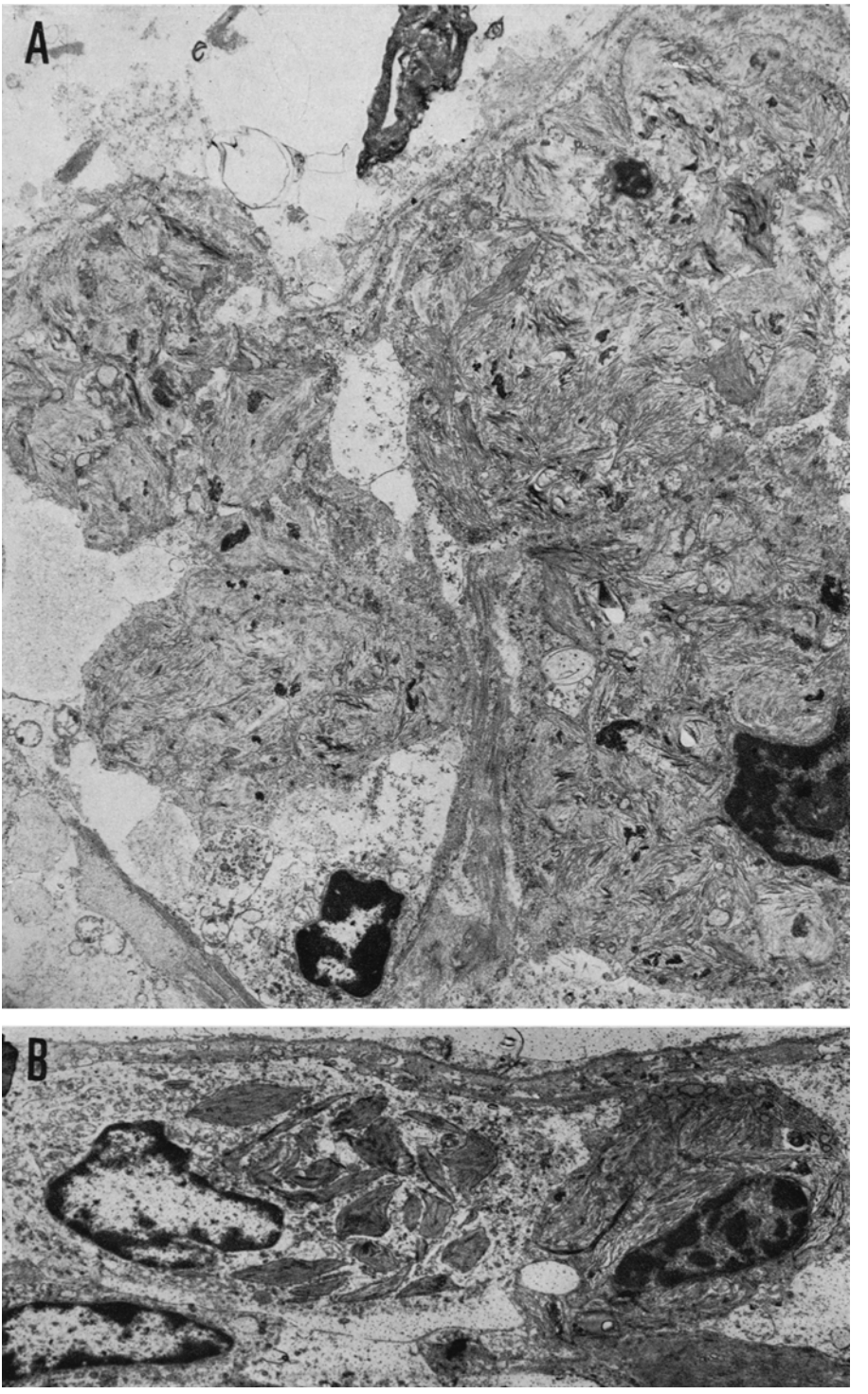

Fig. 3. (A) Perivascular histiocytes and their processes distended by cytoplasmic storage of lamellar material. × 6000. (B) Perivascular histiocytes filled by diffuse accumulation (at right) or circumscribed pleomorphic aggregates (at left) of lamellar cytoplasmic inclusions. × 6000

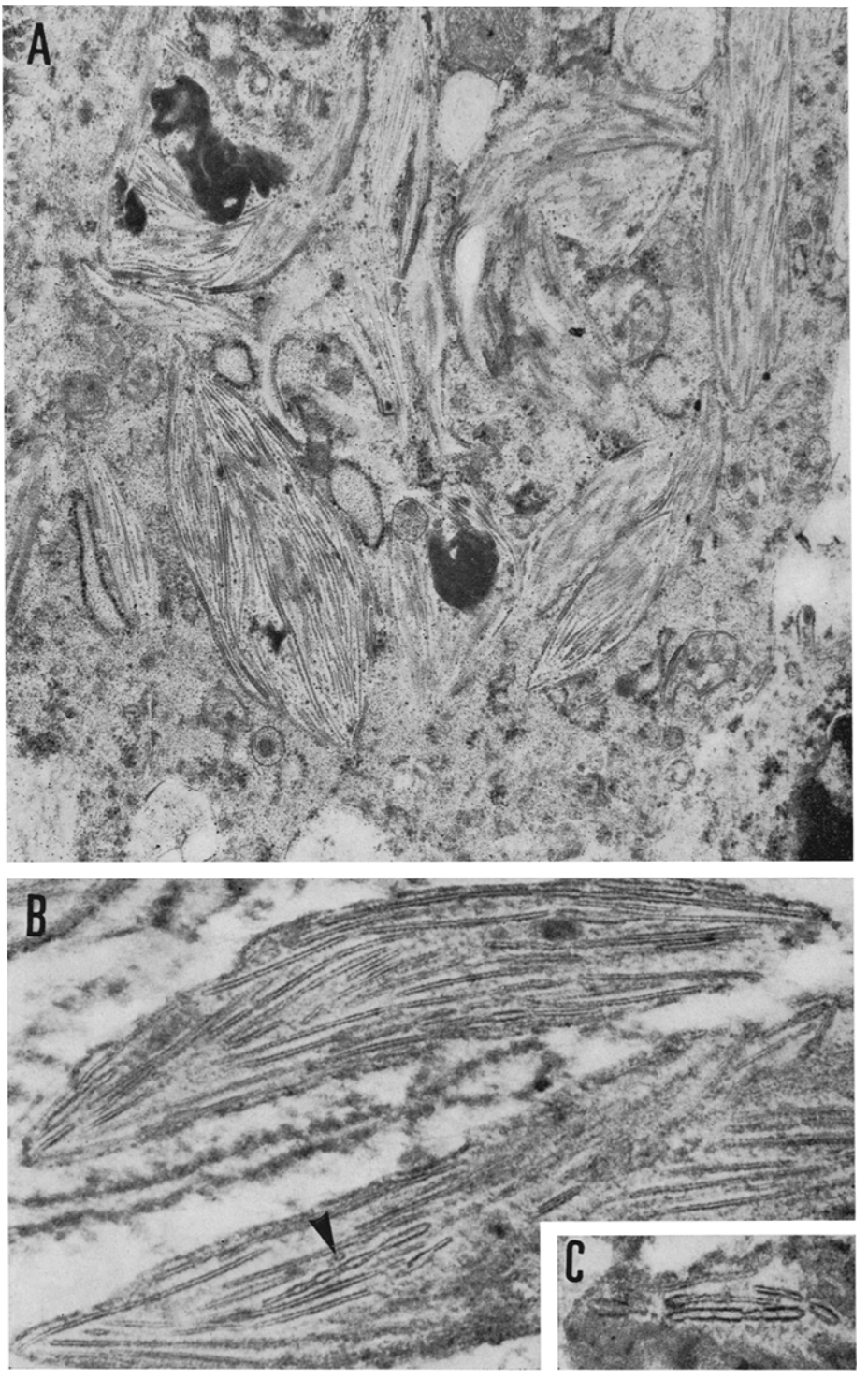

Fig. 4. (A) Cytoplasm of perivascular histiocyte with storage of large amounts of rather regularly orientated lamellar material and some dense bodies. × 24900. (B) Circumscribed aggregates of leaflets consisting of two electron-dense membranes separated by an electron-lucent space which may show occasionally narrower and broader segment (arrowhead).

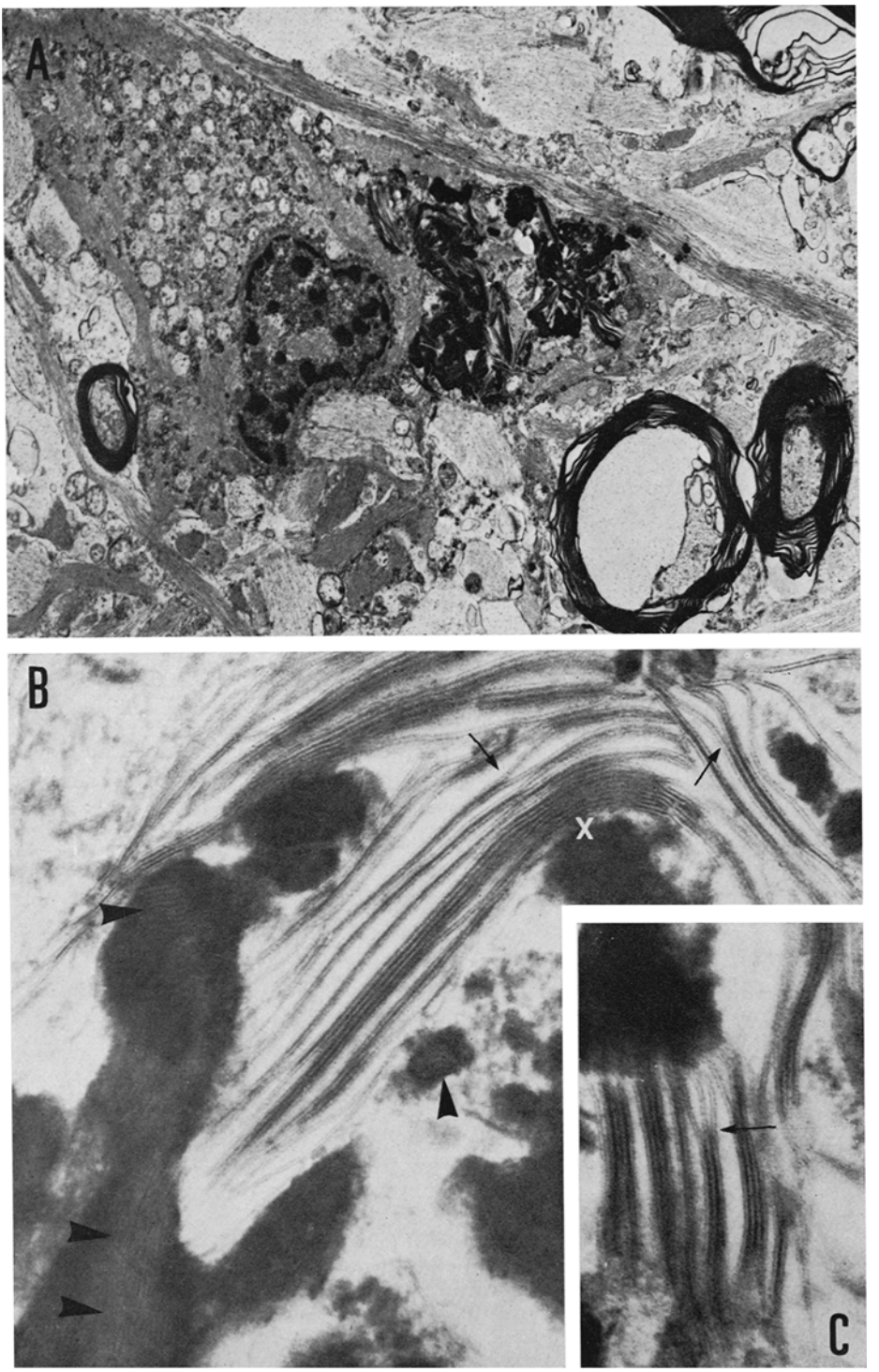

Fig. 5A—C (for legend see p. 246)

up to 200 Å) structures (Fig. 4C). Cross-cut circular profiles could not be identified, thus excluding a tubular character of the parallel structures which may be appropriately designated as "leaflets". Among myelin sheaths which lacked obvious abnormalities (apart from fixational artefacts and autolytic changes), fibrous astrocytes were frequently encountered, sometimes with cytoplasmic accumulation of an electron-dense irregular, partly lamellar material (Fig. 5A). This pleomorphic electron-dense material occasionally demonstrated a fingerprint-like lamellar substructure of 70 Å periodicity (Fig. 5B arrowheads) and showed close contact to linear or curvilinear arrays of compact lamellae with the same periodicity (*X* in Fig. 5B); the dense 40 to 50 Å bands of the compact arrays sometimes split into two separate membranes composing the outer limits of single leaflet-like structures identical to those stored in perivascular histiocytes (Fig. 5B and C arrows). Oligodendroglial cells did not contain leaflet structures or dense material.

Chemical Investigation (Dr. H. Bernheimer, Neurological Institute, Vienna). Thin-layer chromatographic lipid analysis of formalin-fixed material from cerebral gray and white matter, oblongata pyramids and cervical cord revealed no abnormal glycolipid, ganglioside or phospholipid patterns when compared with control tissue.

Discussion

The association of AD with "spastic spinal paralysis" was first mentioned by Neusser and Wiesel (1910), followed by a detailed report by Harris-Jones and Nixon (1959) on spastic paraplegia with AD in two brothers. Hewitt (1957) described two sisters with AD, one of them having spastic lower limbs. Penman (1960) reported on a 28-year-old woman with AD, pes cavus, walking difficulties from the aged 2 years, wasting of leg muscles and exaggeration of all tendon reflexes whereas abdominal reflexes were absent; the father of this patient had died with a paraplegic condition at the same age. Schaumburg et al. (1975) briefly mentioned 2 North American families with AD and spastic paraplegia. In none of these clinical reports were signs of diffuse cerebral involvement mentioned. Our patient presented a clinical picture very similar to these observations; thus it seems that the association of AD with a slowly evolving spinal disorder mainly affecting the pyramidal tracts is more than accidental. However, this clinical picture is entirely different from the symptoms and signs of "classical" ALD in young males which in almost all cases shows initially psychiatric symptoms, then disturbance of gait, hyperreflexia, prominent loss of vision, dysarthria and dysphagia and subsequently spastic tetraplegia with decorticate posturing (Schaumburg et al., 1975). Most juvenile ALD patients do not have clinical signs of adrenal insufficiency (Schaumburg et al., 1975), whereas in all adult cases with spinal disease AD has dominated the clinical picture. It might be that some familial spastic paraplegia patients (Strümpell's disease) without clinical signs of AD will have an ACTH-test positive for AD, thus representing an oligosymptomatic form of the peculiar spastic paraplegia-AD syndrome. On the other hand, it was shown that within an ALD family some members may have only the neurological and

Fig. 5. (A) Astrocyte in white matter with glial fibrils at cell periphery and cytoplasmic accumulation of an electron-dense irregular, partly lamellar material. × 6000. (B) Cytoplasm of astrocyte with pleomorphic electron-dense inclusions occasionally demonstrating a fingerprint-like lamellar substructure (arrowheads). Linear or curvilinear arrays of compact lamellae (*X*) with dense bands sometimes separating into single leaflets (arrows). × 87000. (C) Splitting of compact lamellae at dense band into outer membranes of leaflet structures. × 87000

others only the endocrine abnormalities; this was interpreted as evidence either of a single pleiotropic gene with variable expressivity or of two mutant genes linked on the X-chromosome in the same segment (Chamoles et al., 1971). It is too early to speculate on any genetic pattern of the AD-paraplegia syndrome; however, from the available descriptions it is evident that there are both sporadic and familial cases. In our case, the family history contributed rather little; however, it might be that the skin hyperpigmentation of the patient's mother represents a kind of carrier state, since family studies of "classical" ALD showed that all of 6 obligatory heterozygous women with normal endocrinology had been hyperpigmented at least during several years of their life (Ropers et al., 1975).

Pathological changes of the adrenal glands, considered specific for ALD (Schaumburg et al., 1975), consist of a generalized loss of cortical cells (Blaw, 1970) with adenomatoid nodules of plump eosinophilic cells in some cases (Powell et al., 1975); most prominent are large "ballooned" cortical cells with eccentric hyperchromatic nuclei and cytoplasmic striations (Schaumburg et al., 1972); the cytoplasm is most dense at the periphery of the cell (Powell et al., 1975; Farkas-Bargeton et al., 1967).

The adrenal changes observed by us are consistent with these descriptions. Adrenocortical infiltrations by lymphocytes and mononuclear cells seem to be less constant, being found only in some cases (Powell et al., 1975; Farkas-Bargeton et al., 1967) and they were absent in a series of 17 cases (Schaumburg et al., 1975).

Neuropathological findings in our case correlate well with the clinical syndrome; however, the localization of CNS lesions with restriction to 'pseudo-systemic' incomplete demyelination mainly affecting the pyramidal tracts of the brain stem and spinal cord is markedly different from classical ALD in which the cerebral white matter is mainly involved. It is improbable that spinal involvement is a disease stage preceding the development of cerebral lesions; classical ALD cases do not demonstrate tissue changes suggestive of primary spinal affection, but show Wallerian degeneration of descending brain stem and spinal tracts secondary to diffuse cerebral involvement (Schaumburg et al., 1975). The tendency to affect some tracts more severely than others is not unknown in Krabbe's disease and in metachromatic leukodystrophy (Norman et al., 1963). We found no signs of active demyelination, indicating a very slowly evolving pathological process paralleled by the slow development of clinical signs; this differs from the frequently rather active demyelination and shorter clinical course of classical ALD. Sudanophilic myelin degradation is seen in most ALD cases, but may be absent (Powell et al., 1975). In 14 ALD reports, deposits of PAS-positive material in perivascular cells were mentioned (Powell et al., 1975), leading some authors to classify this form of white matter degradation — when combined with sudanophilia—as "transitional" leukodystrophy (Blaw, 1970). As in our case, peculiar perivascular mononuclear elements intensely stained by PAS are strikingly similar to the epitheloid cell pockets of Krabbe's disease (Lichtenstein and Rosenbluth, 1959).

The neuropathological findings in our case are closely similar to two reports on unclassifiable leukodystrophies: In 1963, Norman et al. reported on two unrelated young boys presenting at autopsy areas of demyelination predominantly in the cerebellar white matter and the long tracts of the brain stem with large numbers of perivascular mononuclear histiocytes filled with insoluble PAS-positive

non-metachromatic lipids; unfortunately, no statement on the condition of the adrenals was made. In 1970, Gullotta et al. reported on three sisters between the ages 4 and 8 years. The one of them presented at autopsy widespread demyelination in the temporooccipital white matter, basal ganglia, brain stem and spinal cord with perivascular pockets of PAS-positive "epitheloid" cells; both adrenals were histologically normal.

Three main problems of ALD have not yet been solved: First, the role of the frequently massive inflammatory infiltrates in the CNS lesions which led to separation of an inflammatory type of diffuse cerebral sclerosis (or Schilder's disease) from primarily degenerative diffuse sclerosis; second, the mechanism of demyelination; and third, the nature of the suggested metabolic defect (Schaumburg et al., 1975).

It is beyond the scope of this paper to comment on the concept of so-called Schilder's disease; however, it should be stressed that in all classical ALD cases, as well as in our observation, perivascular round cell infiltrates have been described in the brain (Powell et al., 1975). Similar infiltrates were found in the adrenals only in 21% of ALD patients (Powell et al., 1975) and only exceptionally in periportal areas of the liver (Farkas-Bargeton et al., 1967). Blood lymphocytosis, thymus enlargement and generalized hyperplasia of lymphatic tissues are well-known features of many AD cases (Neusser and Wiesel, 1910; Anderson and Cleveland, 1966). Therefore, we interpret the widespread lymphocytic infiltrations of various organs in our case as the consequence of adrenocortical insufficiency. Since the majority of classical ALD patients do not manifest clinical evidence of adrenal insufficiency, the absence of major extraneural accumulations of inflammatory cells (Schaumburg et al., 1975) is not surprising. However, the accentuation of inflammatory infiltrates within CNS lesions of ALD is too striking to represent merely a by-product of the clinical manifestation of the endocrine disorder. It was shown that initial changes of the demyelinating ALD lesions are not accompanied by perivascular round cells which on the other hand are most prominent in the center of lesions. This prompted their interpretation as a secondary feature of white matter degeneration (Schaumburg et al., 1975). Similar perivascular lymphocytic cuffs in other types of leukodystrophies like Krabbe's disease and metachromatic leukodystrophy were also regarded as a "resorptive" phenomenon (Gullotta et al., 1970).

The mechanism of demyelination in ALD is still a matter of speculation; however, spongy myelin changes with formation of massive intramyelinic vacuoles similar to certain toxic conditions were mentioned (Schaumburg et al., 1976). Whether this supports the hypothesis of a membrane-stability defect in ALD (Schaumburg et al., 1974) remains to be proven by future studies. Electron microscopy of brain biopsy and autopsy materials from boys with ALD revealed within macrophage cytoplasm paired electron-dense leaflets, each measuring 25—35 Å and separated by an electron-lucent space varying from 40 to 100 Å (Schaumburg et al., 1975); since similar inclusions were found inconstantly also in Schwann cells of a sural and of a capsular nerve of the adrenals, in adrenocortical cells and in interstitial cells of the testes in biopsy materials (Powers and Schaumburg, 1974), these cytoplasmic inclusions were considered as specific for ALD, suggesting a common metabolic disorder (Schaumburg et al., 1975). The leaflet material which we could demonstrate in perivascular brain macrophages and astrocytes

is both in morphology and dimensions identical to that described as specific for ALD; thus, our case can be pathologically classified as ALD. However, we were not able to confirm a close association of these inclusions with lipid droplets (Schaumburg et al., 1975) nor the presence of a prominent perilamellar clear space which is usually found in ALD adrenocortical cells (Schaumburg et al., 1975) but only in some brain macrophages in which the leaflet material is then less apparent (Schaumburg et al., 1974). The extent of cytoplasmic storage of the leaflet material in perivascular histiocytes is outstanding in our case. Evidence of leaflet material in astrocytes is again exceptional since it was stated that these inclusions were not found in oligodendroglial cells or astrocytes (Schaumburg et al., 1975); others confirmed the absence of these structures in astrocytes but were not sure about the oligodendroglial cells (Powell et al., 1975). If the specific storage process were to affect oligodendroglial cells, it would be much easier to understand the demyelinating character of ALD; however, this was not seen in our case. We showed that the leaflet structures originated from more compact linear or curvilinear lamellar profiles by splitting at dense bands within as astrocyte; since there was sometimes a very intimate relationship between the dark fingerprint material, the compact lamellar profiles and the single leaflets, it is probable that these different structures are different steps of one pathological process. The dense fingerprint material is reminiscent of degenerative products of myelin sheaths, suggesting that the leaflet structures may also represent a product of myelin breakdown, which accumulates in ALD in a storage-like manner for as yet unknown reasons; it is possible that the specific metabolic defect is concerned with this particular step of myelin degradation.

Morphological studies have failed so far to contribute much to clarification of the nature of the suggested metabolic defect in ALD (Schaumburg et al., 1975). In our case, the material stored in perivascular histiocytes showed histochemically attributes of an insoluble glycolipid; however, thin-layer chromatographic lipid analysis revealed no abnormalities. Biochemical studies of tissues from ALD patients have so far yielded controversial results (Aguilar et al., 1967; Eviatar et al., 1973; Burton and Nadler, 1974; Powell et al., 1975; Schaumburg et al., 1975). There was no analysis of cholesterol esters and fatty acids in our case; most recently, prominent amounts of abnormal long-chain, mostly saturated fatty acids were found in cholesterol esters of cerebral white matter and adrenal lipids of ALD cases (Igarashi et al., 1976).

In conclusion, the main problems of so-called ALD are yet unsolved; for the clinical and neuropathological presentation of this disease, our observation may add new aspects which might stimulate endocrinologic investigations in some systemic spinal degenerative conditions. Future studies will have to confirm whether the spastic paraplegia-AD syndrome is an adult variant of ALD.

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